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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 26

Serial Number: 09/378,261
Filing Date: August 20, 1999
Appellant(s): Fukodome et al.

Patrea Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to Appellant's brief on appeal filed March 17, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of claims*

The statement of the status of claims contained in the brief is substantially incorrect. Claims 1-15 and 18-23 are canceled. Claims 24-26 are objected to. Claims 16-17 and 27-30 are rejected and are on appeal.

(4) *Status of Amendments After Final*

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct. The claims were last amended in the Amendment filed November 20, 2001. The amendments after final filed on June 27, 2002 and November 26, 2002 have not been entered.

(5) *Summary of invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The Appellant's statement of the issues in the brief is correct.

(7) *Grouping of claims*

Appellant's brief includes a statement that the claims do not stand or fall together. The Examiner would like to draw to the Board's attention that the substitute appeal brief filed 17

April 2003 by Appellant appears to fail to comply with 37 CFR 1.192(c)(8), as it is incumbent upon the Appellant to explain why the claims are believed to be separately patentable. Merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable. If an appealed ground of rejection applies to more than one claim and Appellant considers the rejected claims to be separately patentable, 37 CFR 1.192(c)(7) requires Appellant to state that the claims do not stand or fall together, and to present in the appropriate part or parts of the argument under 37 CFR 1.192(c)(8) the reasons why they are considered separately patentable. The absence of such a statement and argument is a concession by the Appellant that, if the ground of rejection were sustained as to any one of the rejected claims, it will be equally applicable to all of them. See MPEP 1206 Appeal Brief Content (7) *Grouping of Claims.* Furthermore, the Examiner notes that Appellant was informed of this deficiency in the originally filed Appeal Brief by the Notification of Non-Compliance with 37 CFR 1.192(c) (Paper No. 21, filed 11 February 2003). The Examiner did not prepare a second Notification of Non-Compliance with 37 CFR 1.192(c) after the substitute Appeal Brief was filed because of the Examiner's belief that the time period for response from the final rejection (26 March 2002) had expired because the Appellant could pay for an extension of time only up to 26 March 2003 since only a *two* month extension of time was filed with the Notice of Appeal on 08 August 2002, which reduced the maximum extendable period of time from thirteen to twelve months from the date of the final rejection. The Notice of Abandonment for the instant Application was

withdrawn by the granting of Appellant's petition filed under 37 CFR 1.181, filed April 28, 2003. The petition was granted in Paper No. 24, filed July 3, 2003.

It is the Examiner's belief that the rejected claims on appeal should stand and fall together.

(8) ***Claims appealed***

A correct copy of the appealed claims appears as Appendix I: Claims On Appeal on page 17 of the Appellant's Brief. The copy of the Proposed Amended Claims presented as Appendix II: Proposed Amended Claims on pages 18-19 of Appellant's Brief are incorrect as none of the amendments after final have been entered into the instant Application.

(9) ***Prior Art of record***

No prior art of record is relied upon in the rejection of claims under appeal.

(10) ***New Prior Art***

No new prior art is being applied.

(11) ***Grounds of rejection***

The following ground(s) of rejection are applicable to the appealed claims.

1. Claims 16-17 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes methods using antibodies or parts of antibodies to bind to the receptor for endothelial cell protein C/activated protein C (APC) (see pages 21-23). By binding to the APC receptor, the antibodies block the binding of APC to the receptor, thereby inhibiting the biological function of APC. The scientific analogy of the ligand (APC) binding to its receptor is that of a lock fitting into a key, or more accurately because of three dimensionality and protein structure, a hand fitting into a glove. Base claim 16, upon which all of the rejected claims depend from, has the explicit limitation that the compounds used in the instant method block binding of protein C or activated protein C to the receptor by binding to the receptor itself. This limitation is crucial because it excludes methods that use compounds, such as antibodies or receptor fragments, that could inhibit the binding of APC to the APC receptor by physically binding to the ligand, i.e. APC, and therefore prevent the "hand" (the APC ligand) from fitting into the "glove" (APC receptor). In plain language, the claims only encompass compounds that inhibit biological function by binding to the "receptor glove," and exclude compounds that bind to the "ligand hand." By using the receptor as an immunogen, it can be administered as a vaccine and some of the antibodies raised against the receptor would possess the desired biological function of blocking binding of APC.

In contrast, the specification is silent as to how to make receptor fragments that bind to the APC receptor as explicitly required by the limitations of claim 16. Receptor fragments can easily be made that bind to the ligand APC, much like a glove's individual finger, if cut off from the rest of the glove, will still fit an individual finger like a thimble (see pages 32-34 of the instant specification for discussion of soluble receptor fragments). However, receptor fragments do not bind to or "fit" the receptor itself because the receptor has evolved to be selective and specific for the ligand that binds to and activates the receptor in order that one ligand for one biological function does not inadvertently activate a totally different receptor with a totally different biological function. This rejection is especially pertinent to dependent claim 28 which explicitly recites receptor fragments as the compound used in the method of claim 16.

In a similar fashion, the disclosure does not adequately describe nucleic acid sequences inhibiting expression of the receptor, as required by dependent claim 17, which can also bind to the receptor, as required by independent claim 16 as noted above. Nucleic acid sequences that inhibit the expression of a protein product such as the APC receptor are called antisense sequences or antisense oligonucleotides. Antisense oligonucleotides are designed to be complementary in nucleotide sequence to the encoding nucleotide sequence that one wishes to inhibit. The encoding nucleotide sequence in this case is the sequence that encodes the APC receptor. When an antisense sequence binds to its complementary encoding sequence, the targeted encoding sequence cannot perform its biological function of participating in the synthesis of the targeted encoded protein, in this case, the APC receptor. The failure to produce

new APC receptors results in the "downregulation" of receptor number and subsequent inhibition of receptor function due to an actual lowering of the number of receptors produced by the cell (see pages 27-31 of the instant specification). The instant specification is silent as to how to make nucleotide sequences that have the complementary nucleotide structure that can function as an antisense nucleotide sequence and that also possess a ligand structure that somehow would bind to the expressed receptor protein itself, which is completely separate and distinct from the structure required of an antisense nucleic acid that interacts with an encoding nucleic acid to inhibit protein expression.

Finally, the specification fails to provide an adequate written description of "synthetic or natural compounds other than proteins, peptides or nucleic acid sequences which inhibit binding" (claim 17). It is noted that rather than describing the particular or specific chemical structure of the compound used in instant claim 17, the teachings of the disclosure merely allude to what the compound is not and what in general the compound may be (see pages 25-27 of the instant specification). No description is provided of the chemical structure of even a single compound that could be used that meets the limitations of claim 17. Indeed, no description is provided of even the name of a single compound that could be used that meets the limitations of claim 17.

2. Claims 16-17 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibody or antibody fragment immunoreactive with the receptor, does not reasonably provide enablement for any other compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the invention commensurate in scope with these claims. The specification is enabling for methods using antibodies or parts of antibodies to bind to the receptor for endothelial cell protein C/activated protein C (APC) (see pages 21-23 of the instant specification). The specification does not provide sufficient guidance or any working examples on how to make blocking compounds that bind to the receptor other than antibodies or antibody fragments because the blocking of receptor binding by non-antibody compounds is highly unpredictable in the protein arts because a protein's function cannot be adequately predicted from its amino acid sequence. The amino acid sequence of the receptor does not provide the skilled artisan with adequate guidance as to how to make ligands that can block that receptor with any reasonable expectation of success. Antibodies to the receptor that block binding are enabled because the receptor protein can simply be administered to animals in the form of a vaccine and the animal's immune system automatically makes a variety of antibodies, easily purified from serum by those of skill in the art, and some of those antibodies can be reasonably expected to interact with the receptor binding site so that they block binding. However, given just the receptor's amino acid sequence, it would require undue experimentation for the skilled artisan to make from scratch a ligand that could block receptor binding and enhance inflammation because the disclosure does not provide any working examples or sufficient guidance, such as a core chemical structure or amino acid sequence, that possesses the biological properties required by the language of claim 16.

(12) New Ground of Rejection

This examiner's answer contains no new ground of rejection.

(13) Response to argument

1. Appellant's arguments against the rejection under 35 U.S.C. § 112, first paragraph, based on an inadequate written description, are not persuasive for the reasons set forth below.

Appellant argues that two species of the genus method of claim 16 have been reduced to practice by the inventors: use of antibodies to EPCR (the receptor) and the use of TNF (tumor necrosis factor), a protein cytokine (page 13 of Brief). However, Appellant is mistaken as to the biological mechanism of TNF. The instant Application teaches that it does not function by binding to the EPCR as required by the claim language. Instead, TNF acts by lowering the production of mRNA that encodes the EPCR. In other words, it "downregulates" the number of receptors by inhibiting the expression of the receptor (see pages 17-18 of the instant specification). Appellant goes on to argue that soluble EPCR fragments can also be used; however, as the Examiner has previously indicated, soluble receptor fragments used as the active compounds of the instant method are excluded by the claim limitations because receptor fragments do not bind to the receptor as required by the claim language; receptor fragments work by binding to the ligand, APC, thereby rendering the ligand unsuitable to bind its receptor. In other words, receptor fragments work by acting as "sponges" to sop up available ligands and prevent them from binding to the actual functioning receptors located at the cell surface.

Compounds that bind to the ligand have been excluded from the scope of the claims by amendment as indicated by the prosecution history. The first Office Action on the merits (Paper No. 6, filed July 17, 2001) applied art against the claims because there was no specific limitation that the compounds used had to bind to the receptor and not the ligand. The prior art applied described a method that used an antibody that bound to the ligand protein C (Paper No. 6, filed July 17, 2001, page 4). This rejection was dropped after Appellant amended the claims to include the limitation that the compound used in the instant methods was required to bind to the receptor itself and not the ligand.

Appellant also argues that nucleic acid molecules that inhibit expression of EPCR are described in the application as filed. This much is true; however, nucleic acid molecules that inhibit expression of EPCR and bind to the receptor are not described for the reasons set forth above in the written description rejection.

Contrary to Appellant's assertions, only the species of antibodies and antibody fragments are adequately described by the instant specification in a manner that meets all the limitations of the instant claims of enhancing inflammation by using compounds that block the binding of APC to its receptor by binding to the receptor itself.

Appellant cites *Enzo Biochem, Inc. v. Gen-Probe* (Fed. CIr. Apr. 2, 2002) in support of the assertion that the written description requirement has been met. However, to the extent that the *Enzo* court held that a functional description can meet the written description requirement, it did so in accordance with PTO guidelines stating that the requirement can be

met by disclosing "sufficiently detailed, relevant identifying characteristics," including "functional characteristics when *coupled* with a known or disclosed correlation between function and structure ... ." No such correlation has been disclosed here. It is not necessary to give a precise chemical formula or description of a chemical structure when persons of ordinary skill in the art can ascertain what substance is being described. No such ascertaining as to the substance being described is made with particularity in the instant Application as to what the "compound" is that can be used in the instant claims, other than antibodies and antibody fragments.

2. Appellant's arguments against the rejection under 35 U.S.C. § 112, first paragraph, based on scope of enablement, are not persuasive for the reasons set forth below.

Again, Appellant relies on the use of oligonucleotides and receptor fragments to attempt to refute the Examiner's reasoned position that only the use of antibodies and antibody fragments are enabled by the instant disclosure. Once again, it is the Examiner's position that antisense oligonucleotides and receptor fragments do not bind to the receptor as required by the claim language. Receptor fragments bind the ligand, not the receptor. Antisense oligonucleotides bind complementary strands of nucleic acid, again, not the receptor. It is illuminating to note that of all the *post-filing date* art Appellant relies upon to buttress the assertion of enablement (pages 5-6 of the Brief), not a single one of the ten peer-reviewed research papers listed disclose a single species specifically and adequately described in the instant specification that meets all of the

instant claim limitations, with the sole exception being the species of antibodies which the Examiner has previously indicated as allowable.

Appellant also argues that assays are described by which candidate compounds can be screened, such as oligonucleotides and non-antibody blocking compounds that bind EPCR (page 10 of the Brief). Unfortunately, what this essentially calls for is the use of trial and error to attempt to find a compound that will bind to the EPCR, which is the method claimed by the instant Application. It must be remembered, however, that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech*, 108 F.3d at 1366 (quoting *Brenner v. Manso*n, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). Thus, while the need for some experimentation is by no means necessarily fatal, "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Id.* Such detail is lacking here. The specification does describe how to conduct binding assays for compounds that bind the EPCR (pages 17-19 of the instant specification). The specification also describes what to do with any of the identified compounds once they *have* been identified as binding to the EPCR. What the specification does *not* do, however, is provide the necessary link between those two steps: actually finding a non-protein or non-peptide compound that works. It provides little guidance in the way of selecting a particular

compound, or even of narrowing the range of candidates in order to find a suitable compound without the need for undue experimentation.

Appellant contends that computer assisted drug design as described on pages 26-27 of the instant specification only requires routine experimentation to design compounds based on modeling the 3-dimensional structure of an amino acid sequence and designing new drugs to interact with that structure (page 10 of Brief). Appellant is mischaracterizing computer modeling. Note that "the three-dimensional construct typically depends on data from x-ray crystallographic analyses or NMR imaging of the selected molecule. The molecular dynamics require force field data" (page 26 of the instant specification). None of this critical required "reasonable detail" is disclosed in the instant specification. Nor is it found in the prior art or the post-filing art Appellant has cited. In fact, *none* of the references cited by the Appellant on either pages 26-27 of the specification *or* on pages 5-6 of the Brief disclose *any* computer modeling of the EPCR at all. In order for computer modeling to work, the protein structure in question must undergo pain-staking attempts at crystallization with no reasonable expectation of success (as many proteins refuse to crystallize in sufficient quantity and/or purity) so that an angstrom-by-angstrom model of the protein structure can be built in order to test theories of protein-drug interactions. If computer modeling was as routine as Appellant suggests, the need for "shotgun" approaches and random screening of huge numbers of compounds as taught by the instant disclosure (see page 25 of the specification where it describes screening no less than 10^{15} individual nucleotide sequences; that is a thousand trillion in plain English) would be a

work-intensive waste of time since a computer model could routinely select the right chemical formula to interact with the protein structure in question.

Appellant's arguments concerning the methods to produce oligonucleotides as described on page 31, lines 11-31 of the specification in relation to DNA footprinting assays and the binding of DNA to the cell surface of *Bacillus subtilis* (page 10 of Brief) are moot since bacteria do not possess either APC or APC receptors.

Appellant's arguments concerning the high degree of homology of the EPCR to the CD1 receptor family as providing routine experimentation to practice the claimed methods (page 11 of Brief) are not persuasive given the specification's teachings of the binding selectivity of the EPCR. Protein S, factor X, and its active form, factor Xa, failed to displace bound labeled APC, suggesting that there is a specific binding site for APC on the endothelial cell surface (page 11 of the instant specification). Since the binding of APC to the EPCR is so specific that other ligands do not cross-react or interfere with the binding, the high degree of homology does not appear to provide additional guidance for enabling the skilled artisan to select other compounds that can compete for the binding of APC to the EPCR. Had the Appellant provided evidence that there was cross-reactivity between any CD1 receptor ligand and the EPRC that blocked the binding of APC, the grounds for this rejection based on scope of enablement would have been weakened.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

SG

Stephen Gucker

10/20/03

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